REMARKS/ARGUMENTS

Sequence compliance

Citing 37 CFR 1.821 (d) (MPEP § 2422), the Examiner objected to the specification as containing sequences on pages 33, 34, and 47 of the specification that were not identified by SEQ ID NOs. The Applicants respectfully call the Examiner's attention to the Preliminary Amendment and Sequence Listing filed August 26, 2005 which amended the specification to set forth the required SEQ ID NOs.

Accordingly, the Applicants respectfully request that this objection be reconsidered and withdrawn.

Status of the claims

Claims 5, 10, 20, 21, 25 and 26 were undergoing examination. Claims 10 and 21 are herein canceled without prejudice. Claims 5 and 20 are currently amended. Claims 27 to 31 are new. After entry of these amendments, claims 5, 20, and 25 to 31 will be pending.

Claim 10 stood objected to for being dependent on a cancelled claim.

Claims 5 and 20 were objected to because it was allegedly not clear how much of the contacted compound was needed to inhibit viral infection. It was noted that amending the claim to recite "with an effective amount" would obviate the objection.

Claims 5, 10, 20, 21, 25 and 26 were rejected under 35 U.S.C. 112, second paragraph, for being indefinite and failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 21 remain stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement with regard to their possession of the claimed methods using imidazoquinoline or poly I:C.

Claims 5, 20, 21, 25, and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement with respect to the imidazoquinoline subject matter.

Claims 5, 10, 20, 21, 25 and 26 were rejected under 35 U.S.C. 112, first paragraph, for an alleged lack of enablement. The Examiner considered that these claims were enabled for an *in vitro* method for inhibiting a viral infection or viral replication but not for an *in vivo* method.

Support for the amendments to the claims

Claims 5 and 20 were amended to set forth an effective amount of the poly I:C as suggested be the Examiner. These claims were also amended to set forth that the induction of IRF3 increases expression of interferon β. Support for this subject matter is found in the second full paragraph of specification at p. 17 and in Figure 6.

New claims 27 and 29 set forth *in vivo*. Support for this subject matter is found *inter alia* in the specification in the last paragraph of page 26.

New claims 28 and 30 set forth in vitro. Support for this subject matter is found *inter alia* in the specification in the last paragraph of page 26.

New claim 31 finds support in the specification as set forth above for claims 27 and 29. The human recital finds support *inter alia* in the specification at line 25 on p. 26.

Accordingly, the Applicants believe the amendments to the claims add no new matter and respectfully request their entry.

Response to the objection to claim 10

Claim 10 has been canceled in view of the amendments to its intended base claim.

Response to the objection to claims 5 and 20

Applicants thank the Examiner for his suggestion and have amended claims 5 and 20 accordingly. Thus, the Applicants respectfully request withdrawal of the objection to these claims.

Response to the rejection of claims 5, 10, 20, 21, 25 and 26 under 35 U.S.C. 112, second paragraph, for alleged indefiniteness.

Without acquiescing on the merits and in the spirit of expediting prosecution, the Applicants have amended claim 5 to set forth the term corresponding to the acronym IRF3. With regard to the requisite degree of the stimulated induction of IRF3, said degree is in an amount

effective to increase expression of IFNβ and inhibit the viral infection. Accordingly, the Applicants respectfully submit that the claims as amended are not indefinite and respectfully request reconsideration and withdrawal of these rejections.

Response to the rejection of claims 20 and 21 remain stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Office Action alleges that those of skill would not recognize that the inventors had possession of the claimed invention at the time of filing. The rationale for this position is set forth in the Action on p. 5:

> The specification and the claim fail to disclose any specific identifying characteristics that can be used to identify the TLR3lTLR4 and IRF3 pathways that are expected to inhibit a viral infection or replication in a cell for the claimed method. Thus, applicant was not in possession of the claimed genus and the written description requirement is not satisfied. Please note that the Examiner has determined that even, arguendo, the mechanism of inhibiting viral replication were known, Applicants have not demonstrated that imidazoquinoline or poly I:C could be effectively used in such a method.

Without acquiescing on the merits, the Applicants have amended claim 20 to remove the imidazoquinoline subject matter and to further set forth that the stimulated IRF3 induction in turn increases expression of interferon β, IFNβ. The Applicants show that such IFNβ is induced by poly I:C in the specification at Figure 2C and explain its significance further in Figure 2D. The subsequent activation of IFNβ-dependent anti-viral response pathways/secondary response genes is shown in figures 11 and 12. A person of ordinary skill in the art, recognizing that the poly I:C induces IRF3 as shown in Figure 3, which is a known important regulator of the innate immune response (see, in particular, the specification at line 24, page 3) to activate IFNβ antiviral genes (see Figure 12) would recognize that the Applicants were in possession of the invention as claimed, especially as the specification provides a working example of the inhibition of viral replication in Example 5. In that example, poly (I:C)-treated murine bone marrow-derived macrophages were exposed *in vitro* to murine gammaherpes virus 68. The treatment was found to greatly inhibit viral replication (see, paragraph bridging pages 41 and 42). Additionally, NIH3T3 cells exposed to IFNα/β produced by the treated macrophages also were able to

suppress viral replication (see first full paragraph on p. 42). Accordingly, the Applicants respectfully request that the above grounds for rejection be reconsidered and withdrawn.

Response to the rejection of claims 5, 20, 21, 25, and 26 under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the written description requirement with respect to their imidazoquinoline subject matter.

Without acquiescing on the merits and in the spirit of expediting prosecution, the Applicants have amended the base claims to remove the imidazoquinoline recital and respectfully request reconsideration and withdrawal of this grounds of rejection.

Response to the rejection of claims 5, 10, 20, 21, 25 and 26 for an alleged lack of enablement of their *in vivo* subject matter.

The Applicants thank the Examiner for acknowledging that the invention is enabled as to its *in vitro* aspect. As new claims 28 and 30 set forth an *in vitro* limitation, these two new claims are free of this rejection.

Applicants next turn to the enablement of the *in vivo* subject matter embraced by the remainder of the pending claims. Much of the Examiner's remarks concerned enablement of the imidazoquinoline compound subject matter. Without acquiescing on the merits and in order to expedite prosecution, the Applicants have amended the claims to remove the imidazoquinoline recitals. Accordingly, those factors particular to the imidazoquinoline compound subject matter no longer pertain.

The Office Action also contended that the Applicants had not provided any information regarding the identifying characteristics of the TLR3/TLR4 and IRF3 pathways that would be expected to inhibit a viral infection or replication in a cell. In order to address this concern, the Applicants have amended the base claims to set forth that the IRF3 increases expression of IFNβ. This subject matter is set forth in the second full paragraph of specification at p. 17 and the first full paragraph on p. 20 of the specification. Figure 2C of the specification shows that poly I:C increases IFNβ levels and Figure 2D provides a table which teaches that IFNβ is an important cytokine secreted by virus-infected cells which activates numerous anti-viral and anti-growth defense mechanisms. In view of the above, the Applicants submit that the

secondary considerations presented in support of the enablement rejection are now satisfied and next turn to the principal concern underlying the rejection.

The Examiner would construe the term "inhibiting" to mean a *complete* inhibition, *i.e.* viral infection in a cell will not occur. However, as set forth in the MPEP § 2111 claims must be given their broadest *reasonable* interpretation:

> The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999) (The Board's construction of the claim limitation "restore hair growth" as requiring the hair to be returned to its original state was held to be an incorrect interpretation of the limitation. The court held that, consistent with applicant's disclosure and the disclosure of three patents from analogous arts using the same phrase to require only some increase in hair growth, one of ordinary skill would construe "restore hair growth" to mean that the claimed method increases the amount of hair grown on the scalp, but does not necessarily produce a full head of hair.).

Here, the proposed meaning of the term "inhibiting" is clearly contrary to the repeated usage of the term in the specification and the reasonable interpretation to be made by those skilled in the art[1]. For instance, in discussing Figure 3C, the specification recites "As shown in FIG. 3C, LPS treatment potently induced IP10 transactivation. However, this effect was inhibited by both IRF3-DBD and IKB-DA." (see, lines 8 and 9 at p. 39 of the specification). Looking at Fig. 3C it is clear that the referenced inhibition was well short of being complete for either factor. In the more specific context of anti-viral effects, the specification sets forth that the "Activation of the TLR3/TLR4 signaling pathway was also found to *potently* inhibit viral infection by MHV68 through the autocrine/paracrine production of IFNβ." [italics added for emphasis](see, lines 8 and 9 on page 43). The use of the modifier *potently* would be superfluous if the specification used the term *inhibiting* to indicate a complete inhibition. Similarly, in

[1] The ordinary and customary meaning of a term may be evidenced by a variety of sources, >including "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art."<*Phillips v. AWH Corp.*, *>415 F.3d at 1314<, 75 USPQ2d **>at 1327.< See, the MPEP at §2111.01 III at p. 2100-40, Rev. 6, Sept. 2007):

discussing the inhibition of viral replication the specification in the paragraph bridging pages 41 and 42 recites:

> As some of the secondary response genes activated by TLR3 and TLR4 are known to play a role in viral resistance, we next sought to determine if these TLR ligands could directly inhibit the replication of murine gammaherpesvirus 68 (MHV68). BMMs were simultaneously infected with MHV68 (MOI=5) and treated with various TLR ligands (10, 1 or 0.1 ng/ml lipid A, 100 nM CpG, 10 .mu.g/ml PGN or 1, 0.1, or 0.01 .mu.g/ml poly I:C) for 48 hours, and replication of viral proteins was then assayed by western blot analysis. FIG. 6E demonstrates that either lipid A (lanes 4-6) or poly I:C (lanes 8-10) treatment could ***significantly*** inhibit MHV68 replication in a concentration dependent manner, while PGN had a smaller effect (lane 7), and CpG (lane 3) treatment was similar to the media control. During infections performed in the continuous presence of PGN, we repeatedly observed a ***minor*** inhibition in MHV68 replication. This was true whether BMMs were treated with 10 or 20 .mu.g/ml PGN and the inhibition was always ***considerably weaker*** than that caused by either 1 ng/ml lipid A or 1 .mu.g/ml poly I:C. These data indicate that among the TLRs tested, TLR3 and TLR4 are the strongest activators of genes that play a role in resistance to viral infection.

[bolding and italics added for emphasis]. The above-recited phrases of *significantly inhibit*, *minor inhibition*, and *considerably weaker inhibition* makes clear that the specification did not use the term "inhibit" to indicate a complete inhibition. Rather, given the repeated usages of "inhibition" in the specification, a person of skill in the art would readily understand that the "inhibition" represented by the claims need not be a complete or 100% inhibition.

Having now addressed all the principal concerns identified in framing the enablement rejection, the Applicants now respectfully request its reconsideration and withdrawal.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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